From Bioinformatics-based Predictions to Experiments in Cell Biology: Identification of Enzymes That Generate Marks on Microtubules

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Microtubules are long cytoskeletal polymers that form the frameworks of essential organelles (e.g. the mitotic spindle, cilia, centrioles), and serve as tracks for long-range intracellular transport by motor proteins (including transport inside projections of nerves). The building block of microtubules is a dimer of a/b-tubulin. Microtubules are known to be modified post-translationally by several mechanisms that create subsets of modified polymer tracks. The cellular functions as well as the enzymes that generate post-translational marks on microtubules have been largely unknown. Recently, the work from a number of laboratories have allowed for identification of some enzymes that generate marks on microtubules. Enzyme candidates were identified based on biochemical purification as well as by comparing the phylogenomic pattern of the candidate enzymes with the known phylogenomic pattern of tubulin marks. In collaboration with Bernard Eddé and Carsten Janke (CRBM, Montpellier), these approaches have recently allowed us to identify amino acid ligases that generate polymeric marks on tubulin, collectively known as polymodifications: glutamylation and glycylation (Janke et al., 2005, Science 308: 1758-1762; Rogowski et al., 2009, Cell 137, 1076-1087; Wloga et al., 2009, Dev. Cell, 16: 867-876). We showed that polymodifications regulate the length of microtubules inside cilia in diverse species: the ciliated protist Tetrahymena thermophila and zebrafish Danio rerio. Most of the known post-translational marks occur on the surface of microtubules, more precisely on the flexible C-terminal tail domains of tubulin subunits. For this reason, in analogy to the “histone code” model for chromatin, tubulin modifications have been proposed to function as a “biochemical tubulin code” to regulate the binding of microtubule interactors. In support of the “microtubule code” model, recently, we and Kubo and colleagues (University of Tokyo) found that inside motile cilia, a specific conserved tubulin modification, glutamylation, regulates a specific motor protein, the ciliary inner dynein arm (Suryavanshi et al., Curr. Biol., 2010, 20: 441-445; Kubo et al., Curr. Biol. 2010, 20:441-445). Finally, I will discuss our recent progress toward the function and enzymatic mechanism of a highly conserved tubulin modification, acetylation of lysine (K40) on a-tubulin, the marker of axonal microtubules inside neurons and the only tubulin mark that occurs inside the microtubule lumen.